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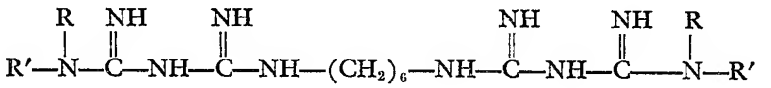
(19)

(54) 1,1'-HEXAMETHYLENE-BISGUANIDINO COMPOUNDS

(71) We, A/S FARMACEUTISK INDUSTRI, a Norwegian joint stock company of Lillogaten 3, Oslo 4, Norway, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to compounds having anti-bacterial activity.

According to the invention there are provided hexamethylene - bis - biguanides of the general formula I:



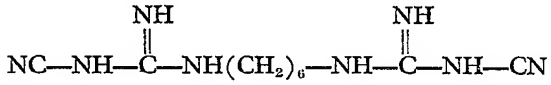
I

wherein R represents hydrogen and R' represents a 2 - hexyl or 2 - heptyl group optionally substituted by a methyl group in any of the 3- to 5- or 3- to 6-positions respectively, a cycloalkyl group having more than 6 carbon atoms, a lower alkyl - cycloalkyl group or a cycloalkyl - lower - alkyl group, or R and R' together with the adjacent N-atom represents an azabicyclo - (3,2,2) - nonane group, and pharmaceutically acceptable acid salts thereof.

As used herein the term "cycloalkyl" comprises mono- as well as polycyclic alkyl groups. The term "lower alkyl" as used herein represents an alkyl group containing 1—4 carbon atoms.

According to another feature of the invention the bis - biguanides may be prepared by a process which comprises either:

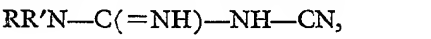
a) reaching hexamethylene - bis - dicyandiamide of the formula



with an amine of the general formula RR'NH wherein R and R' have the above-defined meanings. The reaction may be carried out by melting the reactants together at a temperature in the range 130—180°C, or by using a suitable solvent, or

b) reacting 1,6 - diaminohexane of the formula

with a dicyandiamide of the general formula



wherein R and R' have the above-defined meanings, under conditions corresponding to those indicated under item a).

In general the amine is preferably used in the form of a salt with an inorganic acid in both alternatives a) and b), and hexamethylene - bis - biguanides will then be formed as the corresponding di-salt. The free base may be prepared in an ordinary manner, e.g. by reacting the salt with an equivalent amount of base, such as NaOH or NH_3.

The dicyandiamides employed as starting materials may be prepared by known methods.

The pharmaceutically acceptable acid addition salts of the new hexamethylene - bis-biguanides comprise their salts with one or two equivalents of a suitable acid. A suitable acid addition salt is e.g. a salt of a mineral

acid, e.g. a hydrochloride, hydrofluoride, nitrate, sulfate or phosphate, or a salt with an organic acid, such as a carboxylic acid, e.g. an acetate, benzoate, tartrate, adipate, lactate, maleate, glutamate, ascorbate, citrate, gluconate, oxalate, succinate, pamoate [4,4′ - methylene - bis - (3 - hydroxy - 2 - naphthoate)] or salicylate. The salts may be valuable due to their different solubilities or the therapeutic value of the anion itself. The salts may be prepared from the corresponding base or from salts with other acids by well known methods.

Hexamethylene - bis - biguanides are previously known. Thus, Norwegian patent 83,394 describes a number of compounds in which the terminal groups are substituted phenyl nuclei. One of these compounds, 1,1′ - hexamethylene - bis - [5 - (4 - chlorophenyl)-biguanide], has obtained an extensive use under trade name "chlorhexidine". The substance is primarily used because of its antibacterial effect, and it has been widely used for disinfection of skin and instruments of all types, hand washing, impregnation of wound dressings and storing of sterile utensiles. Odontologists have used the substance for disinfection of e.g. mucous membranes and root channels. It has also been used for treatment of skin infections, eye infections and in gyneacological practice.

One of the newest fields of the use for chlorohexidine is for the prophylactic treatment against tooth and gum diseases. The substance inhibits the formation of the bacterial deposit called plaque, which is considered to be the predominant etiological factor both with respect to caries and gingivitis. Gingivitis occurs after 2—3 weeks if the plaque is allowed to accumulate on the tooth surface, while small decalcifications can be detected after about 4 weeks without oral hygiene. Rinsing of the mouth with chlorohexidine has been found to have a marked inhibiting effect on the formation of plaque and has therefore a prophylactic effect against gingivitis and caries.

In British patent 1,095,902 there is given a general formula comprising an extremely large number of compounds, which are useful as plant fungicides and bactericides. Of the specific compounds mentioned and described in this patent, the one which is most closely related to the compounds prepared according to the invention, is 1,1′ - hexamethylene - bis - [5 - (2 - ethylhexyl)-biguanide], with the generic name alexidine. This is a compound of the above general formula I in which R is hydrogen and R′ is 2 - ethylhexyl, and it is also known for having anti-bacterial activity.

The hexamethylene - bis - biguanides according to the invention, are distinguished from chlorhexidine and alexidine through at least one of the following properties: stronger antibacterial effect, stronger plaque-inhibiting effect or lower toxicity. The compounds are therefore valuable for such uses as, for example those described above for chlorohexidine.

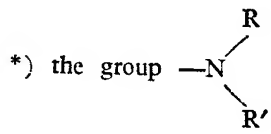
The advantages of the new hexamethylene-bis - biguanides are illustrated by the following test results:

Plaque-Index

Plaque-index was determined on test persons after rinsing with 10 ml of 1.1 mM solution 3 times daily for 3 days. The rinsing was the only type of oral hygiene used during this time.

Plaque-index, which is a recognized measure of plaque-inhibiting property, runs from 0 (no plaque) to 3 (clearly visible plaque).

Compound No.	Compound of formula I R	R′	
1	H	6 - methylhept - 2 - yl	0.36
2		3 - azabicyclo(3,2,2) - non -2 - yl *)	0.58
3	H	cyclohexylmethyl	0.19
4	H	1 - adamantyl	0.36
5	H	2 - norbornyl	0.50
6	H	hept - 2 - yl	0.27
7	H	4 - methylhex - 2 - yl	0.29
8	H	5 - methylhex - 2 - yl	0.70
9 (known)	H	2 - ethylhexyl	0.52

*) the group 

In comparison rinsing with 1.6 mM chlorohexidine under the same conditions gives a plaque-index of 0.75. This figure is itself considerably lower than traditional brushing with tooth paste.

Antibacterial Effect

The inhibition of growth in aqueous solution and sub-cultivation in liquid medium was determined. Reference: Chlorhexidine=1.

Compound	Staph. aureus	Aerobacter aerogenes
1	4	16
2	1	1
3	2	8
4	16	8
5	1/2	1/8
6	4	1
7	8	1
8	8	1
9 (known)	8	2

Toxicity

The cytotoxic effect on human epithelial cells in vitro after treatment for 5 minutes at 37°C was measured. Reference: Chlorohexidine=1.

Compound	Cytotoxic effect relative to chlorohexidine
2	1/8
3	1/2
5	1/8
6	1
7	1
8	1
9 (known)	4

All the tested compounds according to the invention have thus a toxicity lower than or equal to that of chlorhexidine, while alexidine is much more toxic.

Acute Peroral Toxicity in Mice Compound	LD_{50}
Chlorhexidine - digluconate	1800 mg/kg
Compound 1 - dichloride	1690 mg/kg
Compound 4 - dichloride	2830 mg/kg

The compounds of the invention may be used for the same purpose mentioned above for chlorhexidine. Thus, their antibacterial activity may, for example, be utilised for disinfection, in dentifrices and mouth washes and for the treatment of infection in animals and humans.

EXAMPLE 1

7.7 g of 2 - amino - 6 - methylheptane hydrochloride are mixed with 5.5 g hexamethylene - bis - dicyandiamide in a mortar. The mixture is allowed to react at 155°C for 5 hours, is cooled and extracted with boiling water. Upon cooling 1.1′ - hexamethylene-bis - [5 - (6 - methylhept - 2 - yl)-biguanide]dihydrochloride crystallises. The product is recrystallized from methanol - diethyl ether.

Melting point: 225°C

Calculated:

53.69%C 10.05%H 24.08%N 12.19%Cl

Found:

52.17%C 9.95%H 24.23%N 13.83%Cl

EXAMPLE 2

14.5 g of 6 - methylhept - 2 - yl - dicyandiamide are mixed with 6.5 g of hexamethylene - diamine - dihydrochloride and reacted at 155°C for 5 hours. After working as in Example 1 a compound identical to the product described therein is obtained.

EXAMPLE 3

5.6 g of 5 - methylhex - 2 - yl - dicyandiamide and 2.7 g of hexamethylene - diamine - dihydrochloride are melted together and stirred at 155°C for 8 hours. The mixture is then dissolved in boiling water and treated with activated carbon. Upon cooling 1,1′ - hexamethylene - bis - [5 - (5 - methylhex - 2 - yl) - biguanide] - dihydrochloride crystallises.

Melting point: 223°C.

EXAMPLE 4

7.6 g of 4 - methylhex - 2 - yl - dicyandiamide are reacted with 3.6 g of hexamethylene - diamine - hydrochloride for 8 hours at 155°C. After working as in Example 3, 1,1′ - Hexamethylene - bis - [5 - (4 - methylhex - 2 - yl) - biguanide] - dihydrochloride is obtained.

Melting point: 212°C.

EXAMPLE 5

10.2 g of hept - 2 - yl - dicyandiamide and 5.0 of hexamethylene - diamine - dihydrochloride are mixed and heated to 155°C for 7 hours and worked as in Example 3. After recrystallisation from water/ethanol, 1, 1′ - Hexamethylene - bis - [5 - (hept - 2 - yl) - biguanide] - dihydrochloride is obtained.

Melting point: 234°C.

EXAMPLE 6

4.5 g of (1 - adamantyl)dicyandiamide and 1.8 g of hexamethylene - diamine - dihydrochloride are mixed with 10 ml of nitrobenzene and allowed to react at 160°C for 5 hours with stirring. After cooling the sub-

stance is filtered off and recrystallized from ethanol. 1,1′ - Hexamethylene - bis - [5 - (1 - adamantyl)biguanide]dihydrochloride is obtained.

Melting point: 268°C.

Calculated:
57.58%C 8.69%H 22.50%N 11.33%Cl
Found:
56.97%C 8.66%H 22.26%N 12.06%Cl

3.5 g of 2 - aminonorbornane - hydrochloride (norbornane=[2,2,1] - bicyclo - heptane) are mixed with 2.8 g of hexamethylene - bis - dicyandiamide and heated to 155°C for 2 hours. The substance is crystallized from water and recrystallized from methanol/diethyl ether. 1,1′ - Hexamethylene-bis - [5 - (2 - norbornyl)biguanide] - dihydrochloride is obtained.

Melting point: 225°C.

Calculated:
52.87%C 8.50%H 25.67%N 12.99%Cl
Found:
52.11%C 8.59%H 24.02%N 13.01%Cl

EXAMPLE 8

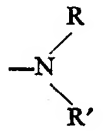
7.8 g of cyclohexane methylamine hydrochloride (hexahydrobenzylamine hydro - chloride) and 6.2 g of hexamethylene - bis-dicyandiamide are mixed and heated to 155°C for 3 hours. The mixture is extracted with boiling water, decolorized with activated carbon, and crystallises upon cooling. The crude product is recrystallized from water. 1,1′ - Hexamethylene - bis[5 - (cyclohexylmethyl)-biguanide] - dihydrochloride is obtained.

Melting point: 216°C.

Calculated:
52.44%C 9.17%H 25.49%N 12.91%Cl
Found:
52.41%C 9.08%H 25.46%N 12.89%Cl

EXAMPLE 9

7.8 g of 3 - azobicyclo(3,2,2)nonane - hydrochloride and 5.8 g of hexamethylene-bis - dicyandiamide are allowed to react at 150°C for 2 1/2 hours. The reaction mixture is worked as in Example 8, and the crude product is recrystallized from methanol/diethyl ether. There is obtained a compound of formula I in which



represents a 3 - azobicyclo(3,2,2) - non - 3 - yl group.

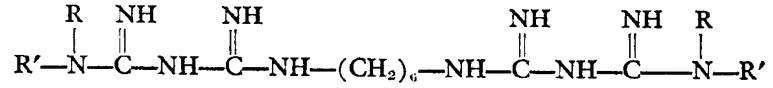
Melting point: 216°C.

Calculated:
54.43%C 8.79%H 24.42%N 12.36%Cl
Found:
52.92%C 8.88%H 24.10%N 11.78Cl%

The identities of all the compounds prepared have been confirmed by IR-spectra.

WHAT WE CLAIM IS:—

1. Hexamethylene - bis - biguanides of the general formula



wherein R represents H, and R′ represents a 2 - hexyl or 2 - heptyl group optionally substituted by a methyl group in any of the 3- to 5- or 3- to 6-positions respectively, cycloalkyl group having more than 6 carbon atoms, a lower - alkyl - cycloalkyl group or a cycloalkyl - lower - alkyl group, or R and R′ together with the adjacent nitrogen atom represent an azabicyclo(3,2,2) - nonane ring, and the pharmaceutically acceptable acid addition salts thereof.

2. A compound according to claim 1, wherein R′ is a 6 - methylhept - 2 - yl group and R is a hydrogen atom.

3. A compound according to claim 1, wherein R′ is a 5 - methylhex - 2 - yl group and R is a hydrogen atom.

4. A compound according to claim 1, wherein R′ is a 4 - methylhex - 2 - yl group and R is a hydrogen atom.

5. A compound according to claim 1, wherein R′ is a hept - 2 - yl group and R is a hydrogen atom.

6. A compound according to claim 1, wherein R′ is a 1 - adamantyl group and R is a hydrogen atom.

7. A compound according to claim 1, wherein R′ is a 2 - norbornyl group and R is a hydrogen atom.

8. A compound according to claim 1, wherein R′ is a cyclohexylmethyl group and R is a hydrogen atom.

9. A compound according to claim 1, in which R′ and R together with the adjacent nitrogen atom form a 3 - azabicyclo(3,2,2)-nonane group.

10. A process for preparing compounds as claimed in claim 1, wherein hexamethylene-bis - dicyandiamide is reacted with an amine of the formula RR'NH wherein R and R' are as defined in claim 1.

11. A process for preparing compounds as claimed in claim 1, wherein 1,6 - diaminohexane is reacted with a dicyandiamide of the general formula

$$RR'N—C(=NH)—NH—CN$$

wherein R and R' are as defined in claim 1.

12. A process as claimed in claim 10 or claim 11 wherein the starting materials are used in the form of their acid addition salts.

13. A process as claimed in any of claims 10—12 wherein the products are converted into the desired acid addition salts.

14. A process for the preparation of compounds as claimed in claim 1 substantially as hereinbefore described.

15. A process for the preparation of compounds as claimed in claim 1 substantially as hereinbefore described with reference to the Examples.

16. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any of claims 10 to 15.

For the Applicants,
FRANK B. DEHN & CO.,
Chartered Patent Agents,
Imperial House,
15—19, Kingsway,
London, W.C.2.

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